REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 40-91 are in this case.

Claims 40-91 were rejected under 35 U.S.C. 103(a) as being unpatentable over Heese et al. (U.S. Patent No. 6,623,759) in view of Bergstrand et al. (U.S. Patent No 5,817,338).

Applicant respectfully traverses these rejections. Claims 40, 48, 65, 83, 90 and 91 have now been amended.

35 U.S.C. § 103(a) rejections

The Examiner has rejected claims 40-90 under 35 U.S.C. 103(a) as being unpatentable over Heese et al. (U.S. Patent No. 6,623,759) in view of Bergstrand et al. (U.S. Patent No 5,817,338). The rejections of the Examiner are respectfully traversed.

The Examiner states that Heese et al. disclose benzimidazole derivative compositions comprising a core and a neutralized enteric coating. Specific benzimidazole derivatives that are deemed suitable for the disclosed compositions include omeprazole, lansoprazole and pantoprazole. Various materials may be used for the enteric coating, including cellulose acetate phthalate and polymethacrylates. The enteric coating is preferably applied as an aqueous dispersion and neutralized to a pH value of around 5.5 to around 7.0. Suitable bases that may be used to neutralize the enteric coating include sodium hydroxide and potassium hydroxide.

The Examiner further states, in response to Applicant's arguments filed 29, September, 2005, that Heese et al. teach a core coated with a polymer layer that is neutralized to a range of pH 5.5 to 7.0, as well as being resistant to gastric acid, which therefore has the functional properties of an enteric coating layer. The Examiner further states that there is no additional layer that exists between the neutralized enteric layer and the core.

The Examiner further states that the instant claims have been interpreted as being drawn to a composition that comprises a substrate in the form of a core that contains the active agent, that is coated with an enteric coating layer neutralized to a pH of at least about 6.5, with no intermediary layer between the neutralized enteric coating and the substrate. However, in the view of the Examiner, an additional outer

coating layer may be included over the neutralized coating layer, and it is this embodiment that is considered as being substantially presented by Heese et al.

According to the Examiner's interpretation of the prior art to Heese et al., the 'intermediate layer' shown in Figure 1 and described in column 5, lines 1-65, constitutes a first enteric coating, such that no intermediate layer is present between this first enteric coating and the core. This is then coated with second enteric coating, as an outer layer, which is a customary enteric, gastric juice resistant layer (column 6, lines 5-9).

The use of at least two enteric coating layers is therefore taught and required by Heese et al., in contrast to the single layer of the present invention. The prior art neither teaches nor suggests a formulation for a benzimidazole having a core and a single, neutralized enteric layer, with no additional enteric coating layers. The possibility of providing a stable formulation for the benzimidazole which does not require the use of an additional, outer enteric coating layer is neither taught nor suggested by Heese et al.

As stated in the present application on page 3, lines 17-19, a disadvantage of formulations which include subcoating layers is that these complicate the manufacturing process and increase the expense and difficulty of manufacture. The present application thus aims to minimize the number of layers involved in a formulation for a benzimidazole. The use of a single solution for application as the enteric coating layer is taught throughout the description and associated examples. For example, page 10, lines 16-23 describes the application of an enteric coating layer with a pH value of at least 6.5 directly to the benzimidazole substrate. No mention is made at any point of the use of more than one solution as an enteric coating. This clearly teaches the use of a single enteric coating layer, that layer being neutralized. The use of an additional, non-neutralized enteric layer is thus excluded.

While continuing to traverse the rejections of the Examiner, Applicant has chosen to expedite the prosecution by amending claims 1, 48, 65, 83 and 90 to clarify that the enteric coating comprises a single enteric coating layer having a pH of at least about 6.5, as supported by the specification at page 7, lines 17-21 and page 10, lines 16-23.

Furthermore, Heese et al. (column 5, lines 1-3) teach that the intermediate layer, which is considered by the Examiner to be equivalent to the enteric coating of

the present invention, has a pH in the range of 5.5 to 7.0, preferably 5.5 to 6.5. Such a coating is therefore mildly acidic. As stated in column 5, lines 51-59 of the prior art, '...alkalilzing additives in the intermediate layer are no longer necessary and can even be damaging, because they increase solubility of the intermediate layer and reduce its protective function.....The more basic equivalents that are present in the intermediate layer, the more protons must penetrate from the outside so that the self repair mechanism of the reactive layer has a quick effect". Hence, Heese et al. clearly teach away from the use of an alkaline intermediate layer.

In contrast, the enteric coating of the present invention is taught as having a pH of at least 6.5, and more preferably in the range of from about 7 to about 10 (page 5, lines 18-19). As stated on page 8, lines 15-19, interaction between the enteric coat and the alkaline core during storage is climinated due to the fact that the enteric coating is not acidic at this stage. As further stated on page 12, lines 20-23, the enteric coatings of the present invention can be applied to the substrate in an aqueous solution if the pH of the solution is adjusted to at least 6.5, and more preferably to an alkaline value, most preferably a value from about 7 to about 10. It is therefore clear that the present invention requires an enteric coating having a basic pH value. This is further demonstrated in Example 1, which provides an enteric coating having a pH of 8.

Claim 40 has been amended to specify that the enteric coating of the present invention has a basic pH, as supported by the specification at page 8, lines 15-19..

With regard to Bergstrand et al., the Examiner states that a multiple unit dosage form of omeprazole is taught, wherein each individual unit comprises a drug core and an enteric coating. The drug core may be formed from inert cores, with the active ingredient layered over the inert core, such as binders. Suitable binders include hydroxypropylmethylcellulose and hydroxypropylcellulose. Suitable enteric coating layer materials include methacrylic acid copolymers, hydroxypropylmethylcellulose acetate succinate, cellulose acetate phthalate, and carboxymethylcellulose. Plasticizers may be included in the enteric coating layers, such as citric acid esters and phthalic acid esters. According to the Examiner, although intermediate layers between the core and the enteric coating layer may be used, the prior art does contemplate embodiments where the enteric layer is applied directly over the drug core (referring to column 5, lines 60-67; and Example 8).

The dosage form of Bergstrand et al. is formed from many pellets, each separately coated with enteric coating, which are then compressed into a tablet. In contrast, the formulation of the present invention comprises a substrate which features the benzimidazole derivative, and a single enteric coating layered over the substrate, as recited in amended independent claims 1, 48, 65, 83 and 90, as well as in previously presented claim 91. The formation of a single enteric layer requires the use of relatively little coating material.

The present invention uses a neutralized enteric coating in order to prevent the known reaction between the alkaline core and the acidic enteric coating occurring in prior art formulations which are devoid of an intermediate layer. This is achieved by converting the acidic functional groups to salts by the addition of a cation (e.g. Na^+), which renders the polymers neutral.

The enteric coatings taught by Bergstrand et al. are not described as being neutralized, and, in fact, there appears to be no component present which is water soluble and provides cations capable of neutralizing the acidic functional groups of the enteric polymer.

Furthermore, the present invention relates to a coating having a basic pH. The enteric coating taught by Example 8 of the prior art to Bergstrand et al. includes methacrylic acid and, thus would be expected to have an acidic pH and therefore does not teach the present invention. Nowhere in this prior art document is it asserted that the enteric coating is not acidic, and the presence of the methacrylic acid copolymer suggests that it may well be. The issue of the effect of pH on the requirement for an intermediate layer is not referred to.

It is therefore clear that the requirement of a neutralized coating having a basic pH is not taught by Bergstrand et al.

While continuing to traverse the rejections of the Examiner, Applicant has chosen to expedite the prosecution by amending claims 1, 48, 65, 83, and 90 to clarify that the enteric coating of the present invention is neutralized. Support for these amendments are provided throughout the specification, such as at page 11, lines 22-23, and page 12, lines 9-14.

Hence, neither of the prior art documents cited either separately or in combination teaches or suggests the use of a single, neutralized layer of enteric coating, having a basic pH, in a formulation comprising a benzimidazole as the active

ingredient, such that the enteric coating is applied directly to the substrate without the use of either an additional outer enteric coating layer, or a subcoating layer applied between the substrate and the enteric coating.

The Applicant considers that amended independent claims 1, 48, 65, 83 and 91, as well as claims 2-47, 49-64, 66-82, and 84-89 respectively dependent therefrom are neither anticipated by nor obvious in light of the cited prior art.

The present response is intended to be fully responsive to all points of objection raised by the Examiner and is believed to place claims 40-91 in condition for allowance. Favorable reconsideration and allowance of the Application is respectfully requested.

Respectfully submitted,

Martin D. Moynihan

Martin Moynihan,
Registration No. 40,338

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